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| <b>(54) Title:</b> TRANSDERMAL PATCH AND METHOD FOR ADMINISTERING 17-DEACETYL NORGESTIMATE ALONE OR IN COMBINATION WITH AN ESTROGEN   |           |   |
| <b>(57) Abstract</b><br><br>Compositions and methods for preventing ovulation in a woman are provided, as well as compositions and methods for female hormone replacement therapy. The compositions can be administered by the use of a transdermal patch. The patch will administer 17-deacetyl norgestimate alone or in combination with an estrogen such as ethinyl estradiol to women.  |           |   |

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TRANSDERMAL PATCH AND METHOD FOR ADMINISTERING  
17-DEACETYL NORGESTIMATE ALONE OR IN  
COMBINATION WITH AN ESTROGEN

Description

Technical Field

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This invention relates to transdermal drug delivery. More particularly, it concerns patches and methods for transdermally administering 17-deacetyl norgestimate either alone or in combination with an estrogen, particularly ethinyl estradiol.

Background

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Combinations of norgestimate (Ngm) and ethinyl estradiol (EE) are administered orally to women as a contraceptive. Bringer J., Am. J. Obstet. Gynecol. (1992) 166:1969-77. McGuire, J.C. et al., Am. J. Obstet. Gynecol. (1990) 163:2127-2131 suggests that orally administered Ngm metabolizes to 17-deacetyl norgestimate (17-d-Ngm), 3-ketonorgestimate, and levonorgestrel (Lng) and that these metabolites may contribute to the pharmacologic response to the orally administered drug.

25

Chien et al., U.S. Pat. No. 4,906,169 describes transdermal patches for co-delivering estrogens and progestins to women for contraception. EE is mentioned as one of the estrogens that may be administered from the patch and Ngm and Lng are mentioned as possible progestins that may be administered.

Applicants are unaware of any art describing the administration of 17-d-Ngm alone or in combination with any estrogen by transdermal or other routes of administration.

#### Disclosure of the Invention

5           This invention provides compositions and a method for preventing ovulation or for providing hormone replacement therapy by the administration of an effective amount of 17-deacteyl norgestimate to a woman. In one aspect, the 17-deacteyl norgestimate is co-administered with an ovulation inhibiting amount of estrogen to the woman. The compositions are preferably administered transdermally.

10           Accordingly, one aspect of this invention is a transdermal patch for preventing ovulation in a woman comprising: a backing layer; and a matrix layer underlying the backing layer, the matrix layer comprising a mixture of 17-d-Ngm and a pressure sensitive adhesive and being adapted to be in diffusional communication with the skin of the woman and to administer an ovulation-inhibiting amount of 17-d-Ngm to said skin.

15           Another aspect of the invention is a transdermal patch for administering 17-d-Ngm and estrogen to a woman, the patch comprising: a backing layer; and a matrix layer underlying the backing layer, the matrix layer comprising a mixture of 17-d-Ngm, an estrogen, and a pressure sensitive adhesive, and being adapted to be in diffusional communication with the skin of the woman and to co-administer an ovulation-inhibiting  
20           amount of said 17-d-Ngm and estrogen to the woman through the skin. These patches are also can be used to provide hormone replacement therapy.

### Modes For Carrying Out The Invention

This invention provides compositions and methods for preventing ovulation in a woman comprising administering and an ovulation inhibiting amount of 17-deacteyl norgestimate. An effective amount can be from about 150 to about 350 µg/day and preferably from about 175 to about 300 µg/day of 17-deacteyl norgestimate. In one aspect, , the 17-deacteyl norgestimate is co-administered with an ovulation inhibiting amount of an estrogen such as ethinyl estradiol. An effective amount is from about 150 to about 350 µg/day and preferably from about 175 to 300 µg/day of 17 deacteyl norgestimate and from 10 to 35 µg/day of ethinyl estradiol.

The transdermal patches of the invention provide contraception for women. They also are adapted for hormone replacement therapy.

The patches are intended to deliver 17-d-Ngm and, optionally an estrogen, to the skin continuously for an extended time period, typically 1-7 days and preferably for 7 days.

When the patches are worn for contraception, a patch will typically be placed on the skin on the fifth day of the menstrual cycle, and replaced as needed until 21 days of wearing have elapsed. For instance, in the case of a 7-day patch, three patches will be required to deliver the drug(s) for the 21-day period. If desired a placebo patch may be worn thereafter until the fifth day of the succeeding menstrual cycle. This regimen is repeated for each menstrual cycle.

17-d-Ngm and estrogens both inhibit ovulation, albeit by separate pathways. 17-d-Ngm inhibits the release of luteinizing hormone (LH), whereas the predominant effect of estrogen is to inhibit the secretion of follicle-stimulating hormone (FSH). Thus, when a combination of 17-d-Ngm and estrogen is administered according to the invention, ovulation is prevented by inhibiting the ovulatory stimulus and/or by inhibiting the growth of follicles. 17-d-Ngm administration is believed to be advantageous relative to

the parent compound (Ngm) or its other metabolites in that 17-d-Ngm inhibits little or no androgenic activity.

5 The effective dose of 17-d-Ngm for inhibiting ovulation is normally in the range of about 150 to about 350 µg/day, preferably from about 175 to about 300 µg/day, and more preferably from about 175 to about 250 µg/day. The patches of the invention will typically have a basal surface area (i.e. the area in diffusional contact with the skin) between 10 and 50 cm<sup>2</sup>. The effective dose of estrogen for inhibiting ovulation will depend upon the particular estrogen being co-administered. For instance, when the estrogen is ethinyl estradiol, the dose will normally be at least 10 µg/day, preferably from  
10 about 10 to 35 µg/day, and most preferably approximately 20 µg/day. The patches will contain sufficient amounts of 17-d-Ngm and, when present, estrogen, to provide such daily doses for the intended patch wear time. Typically, such doses are from about 20 µg/day to about 200 µg/day, and preferably from about 30 µg/day to 150 µg/day of ethinyl estradiol.

15 The patches of this invention are matrix or monolithic-type laminated structures. Such transdermal patches are well known in the art. They comprise a matrix layer of the drug(s) admixed with a pressure sensitive adhesive and a backing layer. The matrix serves as both the drug reservoir and the means by which the patch is affixed to the skin. Prior to use, the patch will also include an impermeable release liner layer.

20 The backing layer is impermeable to the drug and other components of the matrix and defines the top face surface of the patch. It may be made of a single layer or film of polymer, or be a laminate of one or more polymer layers and metal foil. Examples of polymers suitable for use in making backing films are polyvinylchloride, polyvinylidene chloride, polyolefins such as ethylene-vinyl acetate copolymers, polyethylene, and  
25 polypropylene, polyurethane, and polyesters such as polyethylene terephthalate.

The pressure-sensitive adhesive of the matrix will normally be a solution polyacrylate, a silicone, or polyisobutylene (PIB). Such adhesives are well known in the transdermal art. See, for instance, the Handbook of Pressure Sensitive Adhesive Technology, 2nd Edition (1989) Van Nostrand, Reinhold.

Pressure sensitive solution polyacrylate adhesives are made by copolymerizing one or more acrylate monomers ("acrylate" is intended to include both acrylates and methacrylates), one or more modifying monomers, and one or more functional group-containing monomers in an organic solvent. The acrylate monomers used to make these polymers are normally alkyl acrylates of 4-17 carbon atoms, with 2-ethylhexyl acrylate, butyl acrylate, and isooctyl acrylate being preferred. Modifying monomers are typically included to alter the T<sub>g</sub> of the polymer. Such monomers as vinyl acetate, ethyl acrylate and methacrylate, and methyl methacrylate are useful for this purpose. The functional group-containing monomer provides sites for crosslinking. The functional groups of these monomers are preferably carboxyl, hydroxy or combinations thereof. Examples of monomers that provide such groups are acrylic acid, methacrylic acid and hydroxy-containing monomers such as hydroxyethyl acrylate. The polyacrylate adhesives are preferably crosslinked using a crosslinking agent to improve their physical properties, (e.g., creep and shear resistance). The crosslinking density should be low since high degrees of crosslinking may affect the adhesive properties of the copolymer adversely. Examples of crosslinking agents are disclosed in U.S. Pat. No. 5,393,529. Solution polyacrylate pressure sensitive adhesives are commercially available under tradenames such as GELVA™ and DURO-TAK™ from 3M.

Polyisobutylene adhesives are mixtures of high molecular weight (HMW) PIB and low molecular weight (LMW) PIB. Such mixtures are described in the art, e.g., PCT/US91/02516. The molecular weight of the HMW PIB will usually be in the range of about 700,000 to 2,000,000 Da, whereas that of the LMW PIB will typically range between 35,000 to 60,000. The molecular weights referred to herein are weight average molecular weight. The weight ratio of HMW PIB to LMW PIB in the adhesive will normally range between 1:1 to 1:10. The PIB adhesive will also normally include a tackifier such as polybutene oil and high T<sub>g</sub>, low molecular weight aliphatic resins such as the ESCOREZ™ resins available from Exxon Chemical. Polyisobutylene polymers are available commercially under the tradename VISTANEX™ from Exxon Chemical.

The silicone adhesives that may be used in forming the matrix are typically high molecular weight polydimethyl siloxanes or polydimethyldiphenyl siloxanes. Formulations of silicone adhesives that are useful in transdermal patches are described in U.S. Patent. Nos. 5,232,702, 4,906,169 and 4,951,622.

5           Estrogens that may be combined with 17-d-Ngm in the matrix include 17-J-estradiol and esters thereof such as estradiol valerate, estradiol cypionate, estradiol acetate, estradiol benzoate, and EE. EE is a preferred estrogen for use in combination with 17-d-Ngm. EE/17-d-Ngm combinations may favorably effect metabolic parameters such as elevation of serum high density lipoprotein and reduction of the low density  
10           lipoprotein/high density lipoprotein ratio in serum.

          In addition to the pressure sensitive adhesive, 17-d-Ngm, and optional estrogen, the matrix will typically contain sufficient amounts of permeation enhancers to increase the permeability of the 17-d-Ngm and estrogen through the skin and provide fluxes in the ranges described above. Examples of skin permeation enhancers that may be included in  
15           the matrix are described in U.S. Patent Nos. 5,059,426, 4,973,468, 4,906,463 and 4,906,169, and include, but are not limited to lactate ester of C<sub>12</sub> to C<sub>18</sub> aliphatic alcohol, lauryl lactate, oleic acid or PGML. The amount of permeation enhancer included in the matrix will depend upon the particular enhancer(s) used. In most instances then enhancer will constitute in the range of 1 to 20% by weight of the matrix.

20           The matrix may contain other additives depending upon the particular adhesive used. For instance, materials, such as polyvinyl pyrrolidone (PVP), that inhibit drug crystallization, hygroscopic agents that improve the duration of wear, or additives that improve the physical (e.g., cold flow) or adhesive (e.g., tack, cohesive strength) properties of the matrix may be included.

25           The patches described above also are useful for providing hormone replacement therapy. When used to provide hormone replacement therapy, the matrix is constructed so as to provide an effective amount of 17-d-Ngm and estrogen for the intended purpose. Typically, the matrix and therefore the patch is constructed to provide from about 150 to about 350 µg/day, and preferably from about 175 to about 300 µg/day 17-d-Ngm co-



administered with from about 5 to about 45  $\mu\text{g/day}$  and preferably from about 10 to about 35  $\mu\text{g/day}$  of an ethinyl estradiol. In an alternative embodiment, the patch will administer from about 200 to about 350  $\mu\text{g/day}$ , and preferably from about 175 to about 300  $\mu\text{g/day}$  17-d-Ngm co-administered with from about 20 to about 175  $\mu\text{g/day}$  and preferably from about 30 to about 150  $\mu\text{g/day}$  of 17- $\beta$ -estradiol. The patch is applied for 7 days and replaced with a new patch (for 7 days) for the duration of the therapy.

The patches of the invention may be fabricated using procedures known in the transdermal patch art. The procedure will generally involve formulating the matrix (i.e., mixing the adhesive, drug(s), permeation enhancer, and additives, if any), casting the matrix onto the backing or release liner layer, removing solvent from the matrix and applying the backing/release liner layer as the case may be. As is apparent to those of skill in the art, the matrix composition having an effective amount of the drug dispersed therein can be incorporated into various transdermal constructions and therefore, applicants are not limited to the embodiments exemplified below.

The following examples further illustrate the invention. These examples are not intended to limit the invention in any manner. Unless indicated otherwise, stated percentages are by weight.

## EXAMPLES

### Example 1

Duro-Tak 87-2287 is a solution polyacrylate adhesive available from National Starch and Chemical Co. Its monomer composition is: vinyl acetate, 2-ethylhexyl acrylate, hydroxyethyl acrylate, and glycidyl methacrylate. It contains no crosslinking agent. It is available as a 50% solids solution in ethyl acetate.

Mixtures of Duro-Tak 87-2287, 0.26% aluminum acetylacetonate crosslinker, 6% 17-d-Ngm, 1% EE, and various permeation enhancers were prepared. These mixtures were cured and cast as a 100 micron thick (wet) layer onto a 3M 1022 polyester backing and dried. Skin flux tests were carried out on the resulting assemblies according to the

procedure described in col. 7 of U.S. 5,252,334. HPLC was used to assay for 17-d-Ngm and EE. A Perkin Elmer HPLC system with Diodearray detector set at 245 nm and 215 nm for 17-d-Ngm and EE, respectively. The mobile phase was 55% water, 45% acetonitrile at a flow rate of 1.0 ml/min. Retention time was 4.5 and 3.0 min. for 17-d-Ngm and EE, respectively. Details of the formulations and the results of the flux tests are shown in Table 1 below.

Table 1

| <u>Formulation</u> | <u>Flux (<math>\mu\text{g}/\text{cm}^2/\text{hr}</math>)</u> |                    |
|--------------------|--|--------------------|
|                    | <u>17-d-Ngm</u>  | <u>EE</u>          |
| 2% TG + 4% OL      | 0.30 $\pm$ 0.04  | 0.061 $\pm$ 0.007  |
| 2% TG + 10% ML     | 0.39 $\pm$ 0.03  | 0.076 $\pm$ 0.005  |
| 2% TG + 10% PGML   | 0.29 $\pm$ 0.06  | 0.0571 $\pm$ 0.009 |
| 3% TG              | 0.24 $\pm$ 0.06  | 0.043 $\pm$ 0.011  |
| 4% TG + 15% ML     | 0.38 $\pm$ 0.001   | 0.072 $\pm$ 0.002  |

TG = thioglycerol      OL = oleic acid  
 ML = methyl laurate      PGML = propylene glycol monolaurate

## 10 Example 2

Silicone 4202 is a polydimethylsiloxane adhesive from Dow Corning. It was mixed with 17-d-Ngm, EE, 7% PVP (K30 from BASF; dissolved in n-propanol) and various enhancers. These mixtures were cast as a 100 micron thick (wet) layer onto a 3M 1022 polyester backing and dried. Skin flux tests were carried out on the resulting assemblies as in Example 1. The details of the formulations and the results of the flux studies are reported in Table 2 below.

Table 2

| <u>Formulation</u> |             |                         | <u>Flux (<math>\mu\text{g}/\text{cm}^2/\text{hr}</math>)</u> |                   |
|--------------------|-------------|-------------------------|--|-------------------|
| <u>% 17-d-Ngm</u>  | <u>% EE</u> | <u>Enhancer</u>         | <u>17-d-Ngm</u>  | <u>EE</u>         |
| 4                  | 0.5         | 5% ML + 1% TG           | 0.65 $\pm$ 0.09  | 0.069 $\pm$ 0.007 |
| 6                  | 0.5         | 5% ML + 1% TG           | 0.60 $\pm$ 0.04  | 0.043 $\pm$ 0.004 |
| 6                  | 0.5         | 14% PGML                | 0.48 $\pm$ 0.04  | 0.070 $\pm$ 0.01  |
| 6                  | 0.5         | 14% (TC:PGML;<br>80:20) | 0.58 $\pm$ 0.05  | 0.062 $\pm$ 0.01  |
| *4                 | 0.5         | 4% TG + 5% ML           | 0.64 $\pm$ 0.01  | 0.078 $\pm$ 0.01  |
| 4                  | 0.5         | 2% ML                   | 0.51 $\pm$ 0.08  | 0.074 $\pm$ 0.008 |
| 2                  | 0.5         | 2% TG + 2% ML           | 0.71 $\pm$ 0.09  | 0.18 $\pm$ 0.02   |

\*Contains 14% PVP rather than 7% PVP.  
TC = Transcutanol

Example 3

Comparison studies were done on silicone adhesive-17-d-Ngm/EE patches using  
5 two types of PVP: a soluble low molecular weight PVP designated PVP-K30 from  
BASF and an insoluble crosslinked micronized PVP designated PVP-CLM from BASF.

PVP-K30 is dissolved in absolute ethanol. Mixtures of 17-d-Ngm, EE and PVP-  
K30 were prepared and silicone 4202 and methyl laurate were added thereafter. The  
mixture was blended overnight. The mixture was cast on a 3M 1022 liner at a thickness  
10 of 15 mil (wet) and dried at 70°C for 40 min.

PVP-CLM is available as micronized solids. Silicone 4202 and PVP-CLM were  
blended together and then methyl laurate, EE, 17-d-Ngm, and ethanol were added. The  
mixture was blended overnight and cast onto a 3M 1022 liner and dried as above.

Skin flux studies were carried out on the above-described assemblies as in Example 1. The details of these formulations and the results of the skin flux tests are reported in Table 3 below.

Table 3

| <u>Formulation</u>  | <u>Flux (<math>\mu\text{g}/\text{cm}^2/\text{hr}</math>)</u> |                  |
|---|--|------------------|
|   | <u>17-d-Ngm</u>  | <u>EE</u>        |
| 0.1% EE, 1% 17-d-Ngm, 5% ML,<br>7% PVP-CLM, 86.9% silicone    | 0.49 $\pm$ 0.02  | 0.05 $\pm$ 0.002 |
| 0.1% EE, 1% 17-d-Ngm, 5% ML,<br>7% PVP-K30,<br>86.9% silicone | 0.37 $\pm$ 0.07  | 0.04 $\pm$ 0.008 |

5      Example 4

10      PIB solutions were prepared by dissolving VISTANEX L100, Vistanex LM-MS-LC, and polybutene (Indopol H1900) in hexane. Suspensions of PVP-CLM, 17-d-Ngm, EE and various enhancers in ethanol/ethyl acetate were prepared. The PIB solution was added to the drug suspensions and the resulting mixtures were thoroughly blended. The mixtures were cast as a 10 mil thick (wet) layer onto release liners and dried at 70°C for 40 min. Saranex 2015 backing was laminated to the subassembly. Skin flux studies were carried out on these assemblies as in Example 1. The details of these assemblies and the results of the skin flux studies are reported in Table 4 below.

Table 4

| PIB*  | % EE | % 17-d-Ngm | % PVP-CLM | % Enhancer                        | Flux ( $\mu\text{g}/\text{cm}^2/\text{hr}$ ) |                  |
|-------|------|------------|-----------|-----------------------------------|--|------------------|
|       |      |            |           |                                   | 17-d-Ngm                                     | EE               |
| 1:5:4 | 0.3  | 4.0        | 20        | 15, dibutylsebacate               | 0.23 $\pm$ 0.02                              | 0.06 $\pm$ 0.005 |
| 1:5:4 | 0.2  | 1.0        | 20        | 5, AMIFAT                         | 0.32 $\pm$ 0.02                              | 0.05 $\pm$ 0.004 |
| 1:5:4 | 0.2  | 4.0        | 20        | 5, lauric acid N,N-dimethyl amide | 0.33 $\pm$ 0.02                              | 0.04 $\pm$ 0.001 |
| 2:4:4 | 0.3  | 4.0        | 20        | 20, propyl laurate                | 0.35 $\pm$ 0.09                              | 0.06 $\pm$ 0.002 |
| 1:5:4 | 0.2  | 2.0        | 20        | 5, lauramide diethanolamine       | 0.40 $\pm$ 0.05                              | 0.06 $\pm$ 0.001 |
| 1:5:4 | 0.3  | 4.0        | 20        | 15, isopropyl palmitate           | 0.44 $\pm$ 0.06                              | 0.07 $\pm$ 0.001 |
| 1:5:4 | 0.3  | 4.0        | 20        | 15, ethyl oleate                  | 0.46 $\pm$ 0.06                              | 0.10 $\pm$ 0.001 |
| 1:5:4 | 0.3  | 4.0        | 20        | 8, PGIS                           | 0.48 $\pm$ 0.04                              | 0.10 $\pm$ 0.001 |
| 1:5:4 | 0.2  | 2.0        | 20        | 3, oleic acid                     | 0.60 $\pm$ 0.11                              | 0.06 $\pm$ 0.002 |
| 1:5:4 | 0.2  | 3.0        | 20        | 3, oleic acid                     | 0.60 $\pm$ 0.24                              | 0.04 $\pm$ 0.002 |
| 1:5:4 | 0.2  | 2.0        | 20        | 10, PGML                          | 0.59 $\pm$ 0.05                              | 0.09 $\pm$ 0.001 |
| 1:5:4 | 0.2  | 3.0        | 20        | 10, PGML                          | 0.67 $\pm$ 0.07                              | 0.07 $\pm$ 0.001 |
| 1:5:4 | 0.3  | 4.0        | 20        | 8/3, PGML/oleic acid              | 0.79 $\pm$ 0.04                              | 0.14 $\pm$ 0.001 |
| 1:5:4 | 0.2  | 2.0        | 20        | 10/0.5, PGML/oleic acid           | 0.68 $\pm$ 0.09                              | 0.10 $\pm$ 0.001 |

\* Weight ratio of Vistanex L100: Vistanex LM-MS-LC: Polybutene

AMIFAT is derived from glycerin, oleic acid, and 2-pyrrolidone-5-carboxylic acid.

PGIS = propylene glycolisostearate.

Example 5

A composition and matrix suitable for hormone replacement therapy is prepared as follows. 2% 17 $\beta$ -estradiol, 2% 17-deacetynorgetimate, 20% PVP-CLM and 76% PIB adhesive (1:5:2.5:1.5 Vistanex L100:Vistanex LM-MS-LC: Polybutene:Zonester 85FG) is dissolved in a combination of hexane, ethyl acetate, and ethanol. It was cast onto a polyester release liner and dried at 70°C for 45 minutes. A polyester backing was applied prior to the flux study. The flux study was conducted as described as in Example 1.

Table 5

| Steroid                | Flux ( $\mu\text{g}/\text{cm}^2/\text{hr}$ ) |
|------------------------|--|
| 17-d-Ngm               | 0.10   |
| 17- $\beta$ -estradiol | 0.20   |

Example 6

Transdermal patches having a matrix composed of PIB adhesive, PVP=CLM, lauryl or myristyl lactate, 17-d-Ngm, and EE were made as follows:

The 17-d-Ngm and EE were dissolved in ethyl acetate and the PVP-CL and lauryl lactate or myristyl lactate (obtained from ISP VanDYK of Belleville, New Jersey) were added to that solution. A solution of the PIB adhesive (1:5:4 Vistanex L100:Vistanex LM-MS-LC:Indopol H1900) in hexane was added to the steroid solutions with vigorous mixing. N-propanol, at 10% of the PVP-CLM weight, was added slowly to the final mixtures. The mixtures were cast onto a release liner and dried in an oven at 70°C for 40 minutes. The dried matrix weighed 7.5 mg/cm<sup>2</sup>. The matrix-release liner subassembly was laminated to a polyester (Scotchpak 1012) backing. Another subassembly was laminated to a nonwoven polyester layer (Remay 2250). The release liner was removed from the backing assembly and it was applied to the nonwoven layer assembly to give a 5 layer composite of: backing/adhesive matrix/nonwoven/adhesive matrix/release liner.

Skin flux studies were carried out on these patches as described in Example 1. Details of the patches and the results of the flux studies are reported in Table 5 below.

Table 6

| Matrix Formulation  | Skin Permeability | 17-d-Ngm Flux<br>$\mu\text{g}/\text{cm}^2/\text{hr}$ | EE flux<br>$\mu\text{g}/\text{cm}^2/\text{hr}$ |
|---------------------|-------------------|--|--|
| 72.85% PIB          | Low               | 0.23   | 0.02   |
| 20% PVP-CLM         | Medium            | 0.45   | 0.05   |
| 0.15% EE            | High              | 0.82   | 0.08   |
| 5% lauryl lactate   |                   |  |  |
| 70.8% PIB           | Low               | 0.20   | 0.03   |
| 20% PVP-CLM         | Medium            | 0.55   | 0.08   |
| 0.2% EE             |                   |  |  |
| 2% 71-d-Ngm         |                   |  |  |
| 7% lauryl lactate   |                   |  |  |
| 72.8% PIB           | —                 | 0.64   | 0.09   |
| 20% PVP-CLM         |                   |  |  |
| 0.2 EE              |                   |  |  |
| 2% 17-d-Ngm         |                   |  |  |
| 5% myristyl lactate |                   |  |  |

Modifications of the above-described modes for carrying out the invention that are obvious to those of skill in the field of transdermal patches are intended to be within the scope of the following claims.

5

CLAIMS

1. A transdermal patch for preventing ovulation in a woman comprising:
  - a) a backing layer; and
  - b) a matrix layer underlying the backing layer, the matrix layer
- 5 comprising a mixture of 17-deacetyl norgestimate and a pressure sensitive adhesive and being adapted to be in diffusional communication with the skin of the woman and to administer an ovulation-inhibiting amount of 17-deacetyl norgestimate.
2. The patch of claim 1 wherein said amount is 175 to 300 µg/day.
3. The patch of claim 1 wherein the pressure sensitive adhesive is a solution
- 10 polyacrylate, a silicone, or polyisobutylene.
4. The patch of claim 1 wherein the matrix layer contains a skin permeation enhancer.
5. The patch of claim 4 wherein the skin permeation enhancer is selected from the group consisting essentially of a lactate ester of a C<sub>12</sub> to C<sub>18</sub> aliphatic alcohol, oleic acid, and PGML.
- 15 6. The patch of claim 5 wherein the skin permeation enhancer is lauryl lactate.
7. A transdermal patch for preventing ovulation in a woman comprising:
  - a) a backing layer; and
  - b) a matrix layer underlying the backing layer, the matrix layer
- 20 comprising a mixture of 17-deacetyl norgestimate, an estrogen, and a pressure sensitive adhesive and being adapted to be in diffusional communication with the skin of a woman and to co-administer an ovulation inhibiting amount of 17-deacetyl norgestimate and estrogen to said woman.
- 25 8. The patch of claim 7 wherein the pressure sensitive adhesive is a solution polyacrylate, a silicone, or polyisobutylene.
9. The patch of claim 8 wherein the matrix layer contains a skin permeation enhancer:



10. The patch of claim 9 wherein the estrogen is an estradiol.
11. The patch of claim 10 wherein the estradiol is ethinyl estradiol or 17- $\beta$ -estradiol.
12. The patch of claim 11 wherein the estradiol is ethinyl estradiol.
- 5 13. The patch of claim 12 wherein said amount is 175 to 300  $\mu\text{g/day}$  of 17-deacetyl norgestimate and from 10 to 35  $\mu\text{g/day}$  of ethinyl estradiol.
14. The patch of claim 11 where the estradiol is 17- $\beta$ -estradiol.
15. The patch of claim 14 wherein said amount is 175 to 300  $\mu\text{g/day}$  of 7-deacetyl norgestimate and from 30-150  $\mu\text{g/day}$  of 17- $\beta$ -estradiol.
- 10 16. The patch of claim 11 wherein the skin permeation enhancer is selected from the group consisting essentially of a lactate ester of a  $\text{C}_{12}$  to  $\text{C}_{18}$  aliphatic alcohol, oleic acid, and PGML.
17. The patch of claim 16 wherein the skin permeation enhancer is lauryl lactate.
- 15 18. A method of preventing ovulation in a woman comprising administering and ovulation inhibiting amount of 17-deacetyl norgestimate transdermally to the woman.
19. The method of claim 18 wherein said amount is 175 to 300  $\mu\text{g/day}$ .
20. A method of preventing ovulation in a woman comprising co-administering and ovulation inhibiting amount of 17-deacetyl norgestimate and an
- 20 estrogen transdermally to the woman.
21. The method of claim 20 wherein the estrogen is ethinyl estradiol.
22. The method of claim 21, wherein said amount is 175 to 300  $\mu\text{g/day}$  of 17-deacetyl norgestimate and from 10 to 35  $\mu\text{g/day}$  of ethinyl estradiol.
23. A transdermal patch for providing hormone replacement therapy in a
- 25 woman comprising:
- a) a backing layer; and
  - b) a matrix layer underlying the backing layer, the matrix layer comprising a mixture of 17-deacetyl norgestimate, an estrogen, and a pressure sensitive

adhesive and being adapted to be in diffusional communication with the skin of a woman and to co-administer an ovulation inhibiting amount of 17-deacteyl norgestimate and estrogen to said skin.

5           24.     The patch of claim 23 wherein the pressure sensitive adhesive is a solution polyacrylate, a silicone or polyisobutylene.

          25.     The patch of claim 24 wherein the matrix layer contains a skin permeation enhancer.

          26.     The patch of claim 25 wherein the estrogen is an estradiol.

10          27.     The patch of claim 26 wherein the estradiol is ethinyl estradiol or 17- $\beta$ -estradiol.

          28.     The patch of claim 27 wherein the estradiol is ethinyl estradiol.

          29.     The patch of claim 28 wherein the amount of 17-deacteyl norgestimate is from 175 to 300  $\mu\text{g/day}$  and the amount of ethinyl estradiol is from 10 to 35  $\mu\text{g/day}$ .

          30.     The patch of claim 27 wherein the estradiol is 17- $\beta$ -estradiol.

15          31.     The patch of claim 30 wherein the amount of 17 deacteyl norgestimate is from 175 to 300  $\mu\text{g/day}$  and the amount of 17- $\beta$ -estradiol is from 30-150  $\mu\text{g/day}$ .

          32.     The patch of claim 27 wherein the skin permeation enhancer is selected from the group consisting essentially of a lactate ester of a  $\text{C}_{12}$  to  $\text{C}_{18}$  aliphatic alcohol, oleic acid, and PGML.

20          33.     The patch of claim 32 wherein the skin permeation enhancer is lauryl lactate.

          34.     A method of preventing ovulation in a woman comprising administering an ovulation inhibiting amount of 17-deacteyl norgestimate transdermally to the woman.

25          35.     The method of claim 34 wherein the amount of 17-deacteyl norgestimate is about 175 to 300  $\mu\text{g/day}$ .

          36.     A method of preventing ovulation in a woman comprising co-administering and ovulation inhibiting amount of 17-deacteyl norgestimate and an estrogen transdermally to the woman.

37. The method of claim 34 wherein the estrogen is ethinyl estradiol.
38. The method of claim 34 wherein said amount of 17 deacteyl norgestimate is about 175 to 300  $\mu\text{g/day}$  and the amount of ethinyl estradiol is from about 10 to 35  $\mu\text{g/day}$ .

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/09396

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.  
US CL : 424/449

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/449

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category*      | Citation of document, with indication, where appropriate, of the relevant passages                                       | Relevant to claim No.      |
|----------------|--|----------------------------|
| X<br>----<br>Y | US, A, 5,422,119 (CASPER) 06 June 1995, column 6, line 20 and lines 32-33; column 8, lines 22-23; column 5, lines 49-60. | 1-3, 5-14<br>-----<br>1-14 |
| Y              | US, A, 5,376,377 (GALE ET AL.) 27 December 1994, column 6, lines 40-41.  | 1-14                       |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

|   |  |
|---|--|
| * Special categories of cited documents:  | * later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  |
| * "A" document defining the general state of the art which is not considered to be of particular relevance  | * "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone   |
| * "E" earlier document published on or after the international filing date  | * "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| * "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | * "&" document member of the same patent family  |
| * "O" document referring to an oral disclosure, use, exhibition or other means  |  |
| * "P" document published prior to the international filing date but later than the priority date claimed  |  |

|   |  |
|---|--|
| Date of the actual completion of the international search<br>02 SEPTEMBER 1996  | Date of mailing of the international search report<br><b>17 SEP 1996</b> |
| Name and mailing address of the ISA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer<br>EDWARD J. WEBMAN<br>Telephone No. (703) 308-2351   |

Form PCT/ISA/210 (second sheet)(July 1992)\*

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/09396

## A. CLASSIFICATION OF SUBJECT MATTER: IPC (6):

A61M 37/00; A61L 15/24, 15/26, 15/30, 15/38; A61K 9/70, 47/32, 47/34

